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Previews

Orexin Turns Up the Heat on Obesity

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Brown adipocytes burn chemical energy to produce heat for protection against hypothermia and obesity. Sellayah et al. now reveal that a secreted neuropeptide, Orexin, functions a key driver of brown adipocyte differentiation through direct actions on brown adipose precursors.

Brown adipose tissue (BAT) is a thermogenic tissue that expends energy to produce heat in response to cold or a high-calorie diet. Several key transcription factors have been shown to regulate adipocyte differentiation in brown-fat precursors. However, much less is known about the nature of the extrinsic cues that initiate these transcriptional events. In this issue, Sellayah et al. (2011) identify a surprising function for Orexin as a signal for brown-fat precursor cells to undergo differentiation.

BAT oxidizes fat and carbohydrates to produce heat by uncoupling cellular respiration from ATP synthesis (Cannon and Nedergaard, 2004). Though BAT probably evolved to protect mammals against hypothermia, BAT activity also impacts energy balance and thus counteracts weight gain, at least in rodents. In humans, BAT activity is variable but is strongly correlated with leanness (Lidell and Enerbäck, 2010). Thus, there is intense biomedical interest in identifying pathways that control BAT mass and/or activity since these are potential therapeutic avenues to reduce obesity and/or metabolic disease.

Orexins are small excitatory neuropeptide hormones that promote wakefulness and also stimulate energy expenditure via actions in the brain. Sellayah et al. found that Orexin (Ox)-deficient mice became obese despite eating less than their wild-type littermates. While diminished activity and sleepiness presumably accounts for some of the weight gain, Ox-null mice also seem to have an increase in metabolic efficiency. In other words, Ox-deficient animals produce less heat that is not linked to movement. These results prompted the authors to examine the impact of Ox on BAT-mediated thermogenesis.

Ox-deficient mice had strikingly underdeveloped BAT depots, with a severe reduction in lipid content. Molecular analysis indicated that BAT from Ox-deficient mice is poorly differentiated, with drastically reduced expression levels of many key adipocyte- and brown fat-specific genes. In an elegant experiment, defective BAT development in Ox-deficient animals was rescued by treating pregnant dams with recombinant Ox. These data suggest that Ox regulates BAT differentiation and maturation during embryonic and/or fetal stages.

A key question is whether Ox acts on BAT directly or via the central nervous system (CNS). Ox is known to increase sympathetic outflow to BAT and other tissues (Teske et al., 2010). Because the sympathetic nervous system (SNS) activity is intricately linked to BAT development and function (Cannon and Nedergaard, 2004), it would be reasonable to speculate that Ox indirectly stimulates BAT development via efferent signals from the SNS. However, the Ox receptor, Ox1R, was found to be expressed on cultured brown preadipocytes. Importantly, exogenous Ox drove lipid accumulation and cellular differentiation in cultured brown preadipocytes through OxR1; this signal bypassed the requirement for the proadipogenic hormone cocktail that is typically needed to induce terminal differentiation. Therefore, Ox signaling somehow enhances the activity of Pparγ, the master transcriptional driver of adipose cell differentiation. The selective effect of Ox on brown- but not white-fat precursors in vivo suggests that Ox regulates brown adipocyte-specific pathways that stimulate Pparγ function, like Prdm16 and Pgc-1α (Kajimura et al., 2010). In this regard, Ox induces the expression of both Prdm16 and Pgc-1α in preadipocytes. Alternatively, an Ox-like factor may be required to activate a similar transcriptional mechanism in white-fat precursors. Regardless, these results establish a cell-autonomous action for Ox in brown adipose precursors.

Does Ox regulate commitment to the brown adipocyte lineage and/or differentiation? Sellayah et al. suggest that Ox induces commitment since it can drive brown adipocyte-like differentiation in multipotent C3H10T1/2 fibroblasts. However, C3H10T1/2 cells may be precommitted to the brown adipose fate because these cells can acquire some brown-fat characteristics, like Ucp1 expression, during adipogenesis (unpublished data) (Paulik and Lenhard, 1997). More directly, OxR1-deficient brown preadipocytes differentiate into brown-fat cells in response to standard adipogenic inducers. This means that Ox signaling is not required for the specification of brown-fat cell fate. The brown adipocyte lineage arises from embryonic precursor cells that also give rise to skeletal muscle (Kajimura et al., 2010); however, it is not clear when or where committed brown preadipocytes are formed. In any case, Ox does not appear to control a muscle/brown-fat cell-fate decision, but is rather a (or the) physiological driver of brown adipocyte differentiation in committed preadipocytes (Figure 1).

This work raises important questions for future studies. (1) Where is the Ox that acts on brown-fat precursors made? It is not produced by brown adipocytes themselves, and it circulates in the blood

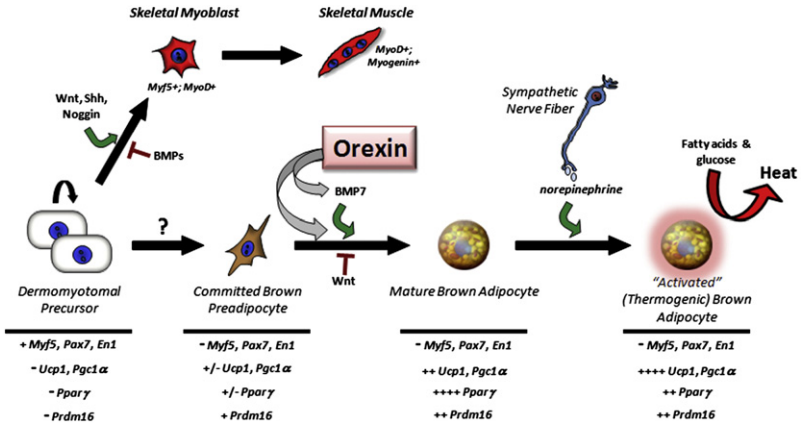

Figure 1. Brown Adipocyte Development and Differentiation

Committed brown preadipocytes arise from precursors in the embryonic dermomyotome that also give rise to skeletal muscle cells. Orexin drives the differentiation of committed brown preadipocytes into mature brown adipocytes, in part through the induction of BMP7 and BMP signaling. Wnt proteins suppress adipogenesis (Kajimura et al., 2010). The thermogenic activity of brown adipocytes is tightly controlled by the sympathetic nervous system. Cold, sensed by the central nervous system, causes the release of norepinephrine (NE) from sympathetic nerve fibers in BAT. NE then binds and activates G protein-coupled β-adrenergic receptors on brown adipocytes; this initiates molecular events that induce respiratory uncoupling (Cannon and Nedergaard, 2004). *Myf5*, *Pax7*, and *Engrailed-1* (*En1*) are expressed prior to brown adipogenic commitment. Adipogenic induction via Orexin strongly induces the expression of adipocyte-specific (e.g., *Pparγ*) and brown adipocyte-specific genes (*Ucp1*, *Pgc-1α*, and *Prdm16*). NE further increases the expression of "thermogenic" genes like *Ucp1* and *Pgc-1α*.

at very low levels. Perhaps Ox expression is activated during a particular stage of embryonic/fetal development in BAT or adjacent tissues. (2) Can Ox stimulate brown adipogenesis in precursor cells from other tissues? For example, is Ox required for the differentiation of brown-like (a.k.a. "Brite" [brown-in-white] or "Beige") adipocytes in white adipose tissue (WAT). (3) What is the mechanism by which the Ox signal is transmitted to the transcriptional pathways of adipogenesis? Sellayah et al. found that Ox functions upstream of BMP7 and BMP receptor to promote adipogenesis. Importantly, BMP7 was previously identified as a critical regulator of BAT development (Tseng et al., 2008), but it has not been reported to be expressed by brown adipocytes. (4) Can extra Ox increase BAT mass in vivo? Does this work in adults? (5) Finally, does a BAT-specific defect account for increased metabolic efficiency in Ox-deficient mice? Ox-deficient animals have a very complicated metabolic phenotype due to the pleiotropic effects of Ox in the brain. It will be important to study energy homeostasis using animal strains that lack Ox function in certain cell types. Notably, Ucp1-deficient mice, with no capacity for BAT thermogenesis, do not gain extra weight under standard conditions—these mice only gain excess weight when living at thermoneutrality (Feldmann et al., 2009). Thus, it seems likely that Ox increases metabolic inefficiency in a BAT-independent manner, perhaps through skeletal muscle.

In summary, Sellayah et al. have identified a novel and important role for Orexin signaling in the regulation of BAT mass. There is good evidence that elevation of BAT function would provide a promising therapeutic avenue to reduce obesity and metabolic disease. It seems unlikely that Ox itself will be a viable therapy, since it has powerful behavioral effects through actions in the brain. However, elucidation of the signaling pathways controlled by Ox in brown adipose precursors may uncover new therapeutic targets to selectively promote BAT expansion.

REFERENCES

Cannon, B., and Nedergaard, J. (2004). Physiol. Rev. *84*, 277–359.

Feldmann, H.M., Golozoubova, V., Cannon, B., and Nedergaard, J. (2009). Cell Metab. *9*, 203–209.

Kajimura, S., Seale, P., and Spiegelman, B.M. (2010). Cell Metab. *11*, 257–262.

Lidell, M.E., and Enerbäck, S. (2010). Nat. Rev. Endocrinol *6*, 319–325.

Paulik, M.A., and Lenhard, J.M. (1997). Cell Tissue Res. *290*, 79–87.

Sellayah, D., Bharaj, P., and Sikder, D. (2011). Cell Metab. *14*, this issue, 478–490.

Teske, J.A., Billington, C.J., and Kotz, C.M. (2010). Acta Physiol. (Oxf.) *198*, 303–312.

Tseng, Y.H., Kokkotou, E., Schulz, T.J., Huang, T.L., Winnay, J.N., Taniguchi, C.M., Tran, T.T., Suzuki, R., Espinoza, D.O., Yamamoto, Y., et al. (2008). Nature *454*, 1000–1004.